PATENT COOPERATION TREATY

20 JUN 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SCHÜSSLER, Andrea
Huber & Schüssler
Truderinger Strasse 246
81825 München
ALLEMAGNE

SCHÜSSLER
Patentanwälte
18. März 2005
Frist: .....

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.03.2005
Applicant's or agent's file reference K 3164 Wd	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/14016	10.12.2003	20.12.2002

Applicant
DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG ...et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tikka, K Tel. +49 89 2399-7830

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference K 3164 Wd	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/14016	International filing date *(day/month/year)* 10.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/47		
Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG ...et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.07.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Armandola, E Telephone No. +49 89 2399-7493

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14016

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-53 as originally filed

Claims, Numbers

1-23 received on 15.12.2004 with letter of 10.12.2004

Drawings, Figures

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: YUAN XUEJUN ET AL: "Multiple interactions between RNA polymerase I, TIF-IA and TAFI subunits regulate preinitiation complex assembly at the ribosomal gene promoter" EMBO REPORTS, vol. 3, no. 11, 20 November 2002 (2002-11-20), pages 1082-1087, XP002238556

D2: MOOREFIELD BETH ET AL: "RNA polymerase I transcription factor Rrn3 is functionally conserved between yeast and human" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 97, no. 9, 25 April 2000 (2000-04-25), pages 4724-4729, XP002143820 ISSN: 0027-8424

Novelty and Inventive step (Art. 33(2) and Art. 33(3) PCT)

Claims 1-23 are considered novel and inventive for the following reasons:

documents D1 and D2 disclose inactive mutants of the transcription initiation factor TIF-IA. Claim 1 also refers to inactive mutants of TIF-IA, but requires that the factor is not or not completely posttranslationally modified. Thus, the subject-matter of claim 1 and all other claims directly or indirectly dependent on it differs from the disclosure of D1 and D2 and is considered novel.

The claims are also considered inventive because the possibility to produce an inactive TIF-IA factor lacking posttranslational modifications or its usefulness to study cell proliferation was not hinted at in any of the available prior art documents.

Re Item VIII

Certain observations on the international application

Claim 21 does not refer as all the other claims to the inactive, non-posttranslationally modified TIF-IA. As the only common feature between claim 21 and the rest of the claims is TIF-IA and this factor was known, it is possible that an objection of non-unity in reference to this claim

may be raised in the regional phase.

Claims

1. A nucleic acid molecule encoding an inactive form of the human transcription initiation factor TIF-IA, wherein said human transcription initiation factor TIF-IA is not or not completely posttranslationally modified.

2. The nucleic acid molecule of claim 1, wherein the serine residue at position 633 and/or 649 is replaced by another amino acid residue.

3. The nucleic acid molecule of claim 2, wherein the serine residue at position 649 is replaced by an alanine residue.

4. The nucleic acid molecule of claim 1, wherein at least one amino acid residue being part of the recognition motif for a phosphatase or kinase comprising the serine residue at position 633 and/or 649 is replaced by another amino acid residue.

5. The nucleic acid molecule of claim 1, wherein the serine residue at position 44 and/or 199 is replaced by another amino acid residue.

6. The nucleic acid molecule of claim 5, wherein the serine residue at position 44 is replaced by an alanine residue or an aspartic acid residue and/or the serine residue at position 199 is replaced by an aspartic acid residue.

7. The nucleic acid molecule of claim 1, wherein at least one amino acid residue being part of the recognition motif for a phosphatase or kinase comprising the serine residue at position 44 and/or 199 is replaced by another amino acid residue.

8. A recombinant vector containing the nucleic acid molecule of any one of claims 1 to 7.

9. The recombinant vector of claim 7 wherein the nucleic acid molecule is operatively linked to regulatory elements allowing transcription and synthesis of a translatable RNA in prokaryotic and/or eukaryotic host cells.

10. The recombinant vector of claim 8 or 9 which is a vaccinia based expresssion vector.

11. A recombinant host cell which contains the recombinant vector of any one of claims 8 to 10.

12. The recombinant host cell of claim 11, which is a mammalian cell, a bacterial cell, an insect cell or a yeast cell.

13. An inactive human transcription initiation factor TIF-IA which is encoded by a nucleic acid molecule of any one of claims 1 to 7.

14. A method of producing an inactive human transcription initiation factor TIF-IA comprising:
(a) culturing the recombinant host cell of claim 11 or 12 under conditions such that said TIF-IA is expressed; and
(b) recovering said TIF-IA.

15. An inactive human transcription initiation factor TIF-IA produced by the method of claim 14.

16. A transgenic non-human animal comprising at least one nucleic acid molecule of any one of claims 1 to 7 or the recombinant vector of any one of claims 8 to 10.

17. A cell line comprising at least one nucleic acid molecule of any one of claims 1 to 7 or the recombinant vector of any one of claims 8 to 10.

18. The transgenic non-human animal of claim 16 or the cell line of claim 17 further comprising at least one wild type allele of the TIF-IA encoding gene.

19. The transgenic non-human animal of claim 16 or 18 which is a mouse or rat.

20. A pharmaceutical composition comprising a nucleic acid molecule of any one of claims 1 to 7, a TIF-IA polypeptide of claim 13 or 15, or a recombinant vector of any one of claims 8 to 10 and a pharmaceutically acceptable excipient, diluent or carrier.

21. A method for identifying compounds capable of inhibiting the conversion of an inactive pre-form of TIF-IA into a biologically active form, said method comprising the steps of:

(a) contacting a cell which expresses TIF-IA and all factors required for said conversion of said TIF-IA with a compound to be screened; and

(b) determining if the compound inhibits the conversion of an inactive pre-form of TIF-IA into a biologically active form.

22. Use of a nucleic acid molecule of any one of claims 1 to 7, a TIF-IA polypeptide of claim 13 or 15, or a recombinant vector of any one of claims 8 to 10 for the preparation of a medicament for treatment of a disease which is associated with an increased cell proliferation.

23. Use according to claim 22, wherein the disease is a tumor.